Pathogenic germline variants in a pediatric cancer cohort and identification of new candidate cancer predisposition genes

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Background

The frequency of pathogenic germline variants in cancer predisposition genes is estimated to be ~8-10% in pediatric cancer populations (Zhang et al. 2015 *NEJM*; Grobner et al. 2018 *Nature*) and have been detected in several different cancer types (Figure 1).

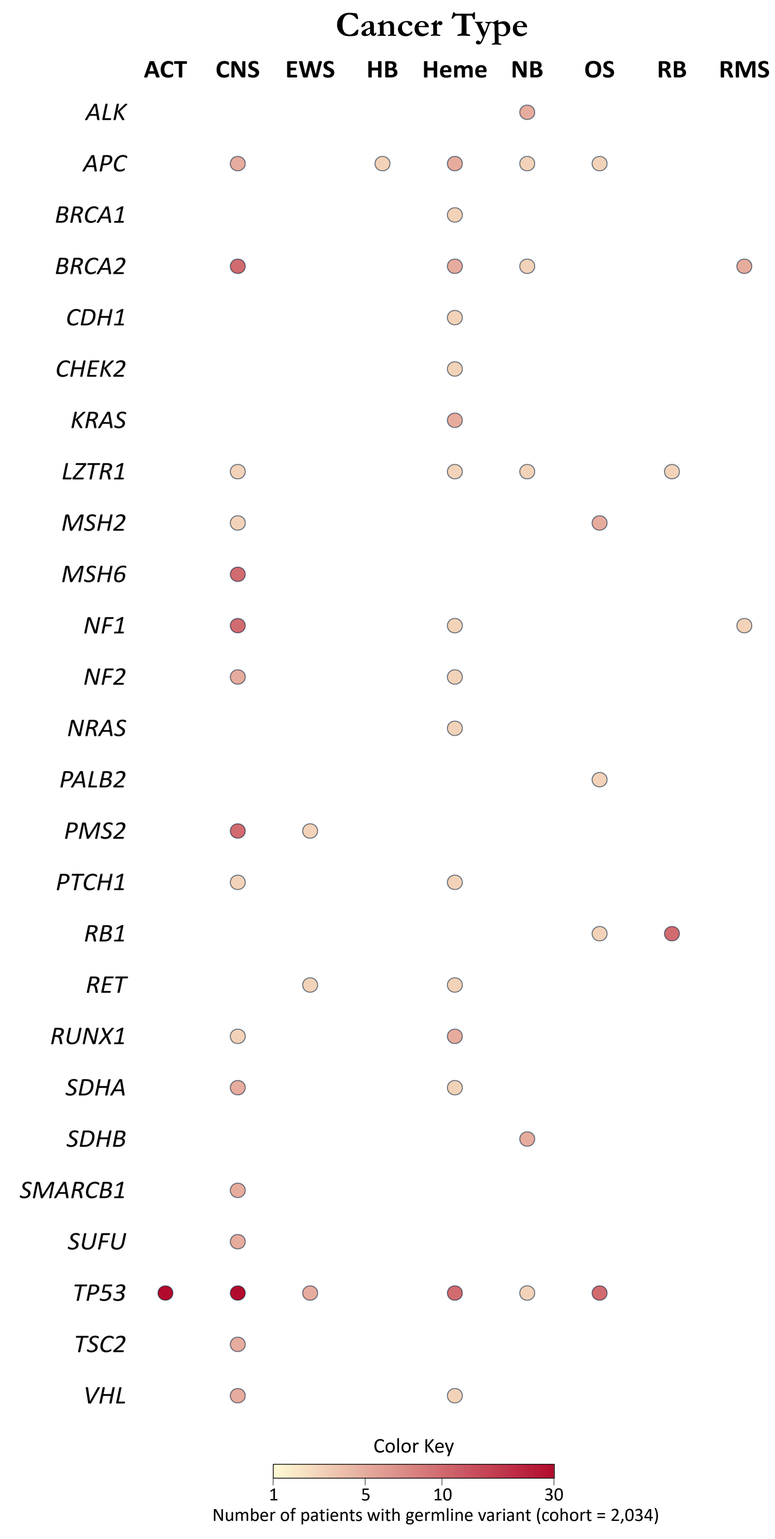

Figure 1: Number of pathogenic germline mutations (SNVs/indels) in predisposition genes (rows) identified in pediatric patients with different cancer types (columns). Data taken from two landmark studies in 2,034 patients (Zhang et al. 2015, Grobner et al. 2018). ACT, adrenocortical tumor; CNS, central nervous system tumor; EWS, ewing's sarcoma; HB, hepatoblastoma; Heme, leukemia/lymphoma; NB, neuroblastoma; OS, osteosarcoma; RB, retinoblastoma; RMS, rhabdomyosarcoma

Objective

The Institute for Genomic Medicine at Nationwide Children's Hospital (Columbus, OH, USA) initiated a translational protocol to evaluate the genomic landscape of pediatric cancers in a focused N-of-1 manner (Figure 2). We applied exome sequencing to search for germline variants in bona fide cancer genes and to identify putative cancer predisposition genes.

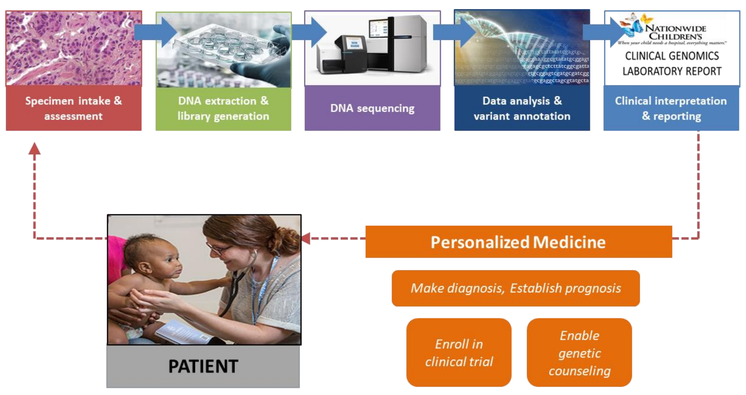

Figure 2: Cancer protocol workflow

Methods

We performed exome sequencing on both tumor (mean depth ~194x) and germline (mean depth ~215x) samples and used SnpEff plus custom in-house scripts for gene and variant annotation.

SNVs and indels were assessed for pathogenicity using the current ACMG/AMP variant interpretation guidelines (Richards et al. 2015 *Genet Med*).

Patient Cohort & Germline findings

Our cohort (N = 45) included 38 patients with central nervous system (CNS) tumors, 5 patients with non-CNS solid tumors, and 2 patients with hematological malignancies (Figure 3).

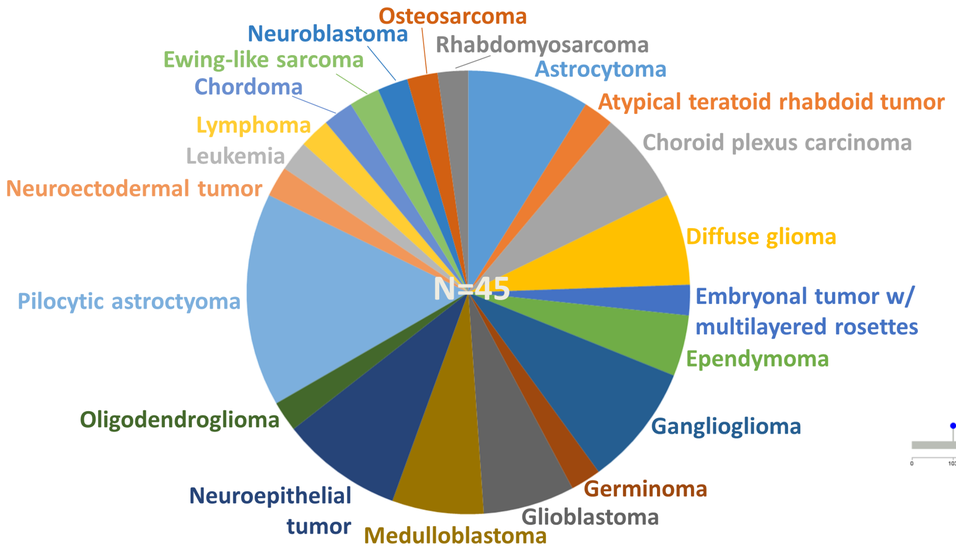

Figure 3: Study cohort

Six patients (13.3%) harbored pathogenic germline variants in well-established cancer predisposition genes *TP53* (3 patients), *NF1* (2 patients), and *PALB2* (1 patient).

Four patients (8.9%) harbored rare, likely damaging missense variants in previously implicated cancer genes *PMS2* (1 patient), *SMARCA4* (2 patients), and *ALK* (1 patient) (Table 1).

Table 1: Summary of pathogenic or likely damaging germline variants in known cancer genes detected in our study cohort.

Age (y) at diagnosis	Sex	Diagnosis	Germline findings
1	M	CPC	†TP53:NM_001276696.1: c.799C>T;p.R267*
4	M	CPC	†TP53:NM_001276695.1: c.625C>T;p.R209W
3	M	CPC	†TP53:NM_001126114.2: c.797G>A;p.G266E
11	F	Astrocytoma	†NF1:NM_000267.3: c.1318C>T;p.R440*
4	F	PA	†NF1:NM_001042492.2: c.1149C>A;p.C383*
6	M	PA	†PALB2:NM_024675.3: c.3175delG;p.V1059fs
17	M	Glioblastoma	•PMS2:NM_000535.5: c.137G>T;p.S46I
4	F	Lymphoma	•SMARCA4:NM_003072.3: c.1886C>T;p.T629I
15	F	Ependymoma	•SMARCA4:NM_001128848.1: c.778A>C;p.M260L
4	F	PA	•ALK:NM_004304.4: c.3362G>A;p.G1121D

CPC, choroid plexus carcinoma; PA, pilocytic astrocytoma
†Pathogenic
•Likely damaging

Candidate Predisposition Genes

We searched for genes in which at ≥2 patients harbored a very rare, damaging or loss-of-function variant, nominating four novel cancer predisposition genes involved in chromatin remodeling (*KAT6B*), DNA repair (*POLI*), and cell signaling (*TXK* and *PTPRF*) (Table 2, Figure 4).

Table 2: Summary of candidate germline variants.

Age (y) at diagnosis	Sex	Diagnosis	Candidate variant	gnomAD frequency	CADD score
		KAT6B			
15	M	Medulloblastoma	p.Y465C	1.8e-5	26.2
14	M	Ganglioglioma	p.R1320H	1.6e-5	24.6
		POLI			
20	M	Osteosarcoma	p.R693fs	1.3e-4	n/a
7	M	Medulloblastoma	p.Q66*	4.5e-5	38.0
		TXK			
14	M	Glioblastoma	p.S178*	0	41.0
3	M	ETMR	p.A172S	1.6e-4	22.9
13	F	Ganglioglioma	p.P74R	0	25.9
		PTPRF			
6	M	Diffuse glioma	p.V254M	0	32.0
1	F	ATRT	p.G1402R	1.6e-5	33.0

ATRT, atypical teratoid rhabdoid tumor; ETMR, embryonal tumor with multilayered rosettes; CADD, combined annotation dependent depletion

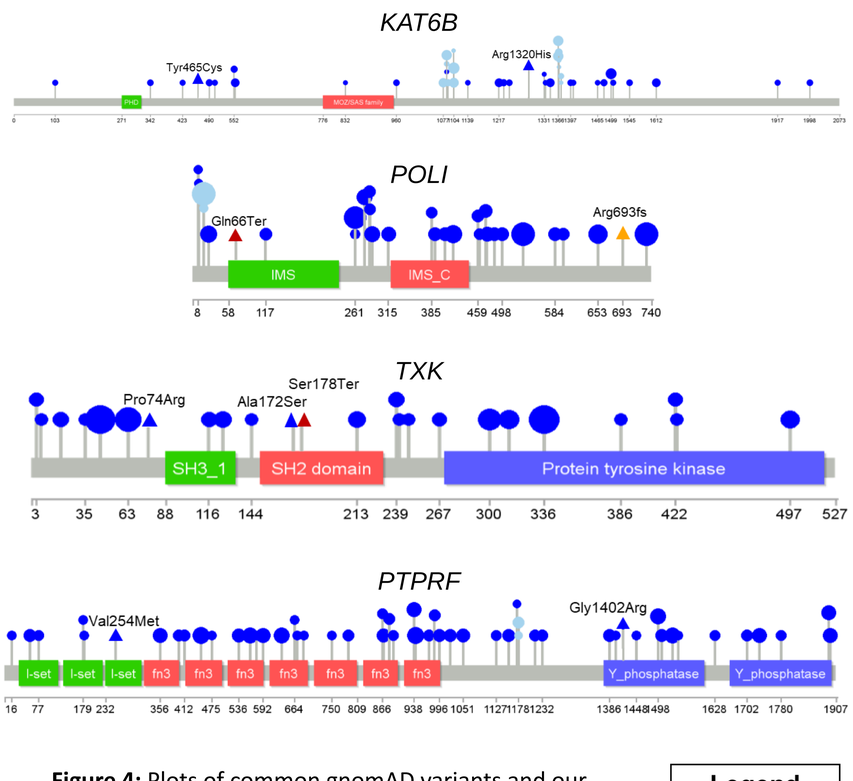

Figure 4: Plots of common gnomAD variants and our cohort variants identified in candidate cancer predisposition genes. Plots were produced with data from gnomAD release r2.0.2 using Lollipops v1.3.2. gnomAD variants with MAF > 0.0001 are plotted, with the size of the circle relative to the MAF.

Discussion

Detection of germline pathogenic variants and identification of new cancer predisposing genes may increase our understanding of tumorigenesis, influence clinical management, and prompt further genetic testing for the patient and families.

Acknowledgements

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